REMARKS

By way of the instant amendment, claims 1-4 and 12-15 have been canceled. Thus, claims 1-15 are now canceled. Further, new claims 16-26 are added.

Rejections Under Section 112

Claims 1-4 and 12-15 stand rejected under 35 U.S.C. 112, first paragraph. The Examiner questions the enablement of the specification. As part of this analysis, the Examiner characterizes the state of the art by saying that the art teaches that the analyte is labeled with a magnetic particle coated with a binder that binds to the analyte. Then the mixture is separated by a magnetic field. After that, a fluorescent or color label is added and detection occurs. The Examiner also questions whether a binder is necessary and thus should be claimed. Further, the Examiner questions how the magnetic field again separates the bound and the unbound magnetic labels and asserts that the magnetic field would attract both the bound and unbound labels.

The Examiner's rejections are respectfully traversed.

Various methods of immunoassay which utilizes the antibody/antigen reaction and which uses an optical label such as a fluorescent label and a color label are well known in the prior art. The present invention was made on the basis of the new idea of using the magnetic label in place of the optical label in the well-known methods of immunoassay which utilizes the antibody/antigen reaction, and with the object of achieving a high sensitivity and a high accuracy in the new method of immunoassay using the magnetic label in place of the optical label. Thus, in applicant's invention, no fluorescent or color labels are utilized.

For the high sensitivity, the present invention uses the SQUID, and for the high accuracy, the present invention detects the magnetized magnetic material labeled analyte by the SQUID which is positioned or directed to detect the magnetic field component which is at a right angle to the magnetic field which magnetizes the magnetic material label.

In the example shown in Fig. 6, first, by means of the antibody/antigen reaction, a second antibody 13 is bound to an antigen 11 fixed to a support 1 by a first antibody 12, and

thereafter, a third antibody 14 labeled with a magnetic material 14a is bound to the second antibody 13 by means of the antibody/antigen reaction.

As mentioned above, the present invention is based on the idea of using the magnetic label in place of the optical label in the well-known methods of immunoassay which utilizes the antibody/antigen reaction. In the methods of immunoassay which utilizes the antibody/antigen reaction, it is a well-known matter that a washing is carried out after completion of each reaction step. The washing step is so well known that it is generally omitted or only briefly mentioned from technical papers. Attached hereto, for example, is a book entitled "Monoclonal Antibody" by Iwasaki, *et al.*, published in 1983. Only selected pages have been translated since the book is quite long, but a translation on page 147-148 shows that it is well known to perform a rinsing step or washing step after each reaction step.

Therefore, in the example shown in Fig. 6, after the second antibody 13 is caused to be bound to an antigen 11 (fixed to a support 1 by a first antibody 12), by means of the antibody/antigen reaction, a washing is carried out to completely remove the second antibody 13 that is not bound to the antigen 11. Thereafter, the third antibody 14 labeled with magnetic material 14a is caused to be bound to the second antibody 13 by means of the antibody/antigen reaction, and then, as a matter of course, a washing is carried out again to completely remove the third antibody 14 that is not bound to the second antibody 13. Therefore, when the magnetizing magnetic field is applied, only the third antibody 14 (labeled with magnetic material 14a) remains. The example shown in Fig. 6 is the embodiment of the present invention applied to a so-called "2-antibody sandwich method" (or double-antibody two-side immunometric method), which is well known in the art.

The "2-antibody sandwich method" is one of various known methods of immunoassay which utilizes the antibody/antigen reaction, and it is a matter of course that the present invention can be applied with no specific problem to known methods of immunoassay which utilizes the antibody/antigen reaction, other than the "2-antibody sandwich method". For example, the present invention can be applied with no difficulty to a method of immunoassay in which a third antibody 14 labeled with magnetic material 14a is caused to be directly bound to an antigen 11 (fixed to a support 1 by a first antibody 12), by means of the

antibody/antigen reaction. Namely, the second antibody (i.e., that the Examiner terms ""binder") is not necessarily required in all situations.

Since a washing step is used, between the various process steps, the magnetic field is not required to distinguish between bound and unbound magnetic material labels. Indeed, applicant's invention does not require the magnetic filed to make such a distinction.

In view of the explanation set forth above and the revision of applicant's claims as explained below, it is submitted that applicant's claims are in full compliance with the provisions of 35 U.S.C. 112.

Prior Art Rejection

The Examiner continues to reject claims 1-4 and 12-15 under 35 U.S.C. 102(e) as anticipated by Witches (6,027,946). While the rejected claims have now been canceled, it is appropriate to discuss the Weitschies patent and how applicant's newly submitted claims distinguish therefrom.

As mentioned above, Weitschies utilizes the magentorelaxometric detection. Namely, after the application of the magnetizing field is stopped, the relaxation of the magnetization is measured. On the other hand, in the present invention, the magnetic field is detected while applying the magnetizing field. This is an important difference, and makes the present invention patentably distinguishable form Weitschies.

In addition, the present invention is characterized by detecting, by use of the SQUID, the magnetic field component which is at a right angle to the magnetic field which magnetizes the magnetic material label.

This feature is neither disclosed nor suggested by Weitschies, since it is impossible to specify the directional relation between the direction of the sample magnetizing field and the direction of the magnetic flux detected by the SQUID, from Fig. 1 of Weitschies.

In order to more particularly define applicant's invention over the Weitschies teaching, applicant has added a new independent claim 16 which recites a method for

immunoassay with a magnetic material label and a Superconducting Quantum Interference Device (SQUID). the method comprising preparing an analyte labeled with said magnetic material label. As an example, the analyte may be the antibody 14 shown in Figure 6. The next step of claim 16 recites applying said analyte labeled with said magnetic material label, to an antigen fixed to a support so that said analyte is bounded to said antigen by means of an antibody/antigen reaction. In reference again to Figure 6, the analyte 14 is labeled with the magnetic material label 14a and is applied to the antigen 11 which is fixed to the support 1. The analyte is bound to the antigen by means of the antibody/antigen reaction. The antibody 14 may be bound directly to the antigen through the antibody/antigen reaction or may be bound through and intermediate antibody 13. The next step in applicant's claim 14 recites magnetizing the magnetic material label on the analyte bounded to the antigen by a magnetic field thereby forming a magnetized magnetic material labeled analyte. Applicant's claim goes on to recite that while one continues to apply the magnetic field which magnetizes the magnetic material label, one detects the magnetized magnetic material label by sensing, using the SQUID, a magnetic flux component which is generated from the magnetized magnetic material label and which is at a right angle to the direction of the magnetic field which magnetizes the magnetic material label. This particular orientation is shown in applicant's Figure 1 in which the analyte 2 is moved in a direction from left to right in the Figure but the magnetic flux is measured in a direction perpendicular thereto.

Applicant's newly submitted independent claim 20 contains similar limitations.

It may be seen from the above newly recited claims that applicant's invention performs a measurement of the magnetic flux while the magnetic field is on and while the analyte is moving through the magnetic field. This technique is neither disclosed nor made obvious by Weitschies which turns off the magnetic field and utilizes a relaxation method to measure the magnetization. Moreover, with regard to orientation of the field, the high level drawing of Weitschies does not make the SQUID orientation clear. It appears that the sample is moved upward from the bottom of Figure 1 so that it is placed within the magnetic field produced by the magnetizing coils. However, since the magnetizing field is turned off during the measurement, the Weitschies structure cannot meet applicant's claimed invention which requires the magnetizing field to be on during the measurements. Not only does

applicant's claims require that the magnetizing field be on but the direction of the magnetizing field must be at right angles to the direction of the measured flux. Weitschies simply does not disclose such structure nor operation. As such, the Weitschies reference may not be utilized as a section 102 rejection. In order for a reference to anticipate applicant's claims, the reference must disclose each and every limitation recited. This is certainly not the case here and thus the Weitschies reference must be withdrawn.

It is submitted that the application is now in condition for allowance and an early indication of same is earnestly solicited.

Respectfully submitted,

Date December 17, 2003

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